

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hoffmann Udo, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med 2012;367:299-308. DOI: 10.1056/NEJMoa1201161

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Supplement Information to the Manuscript Body

Methods

Study Design and Oversight

Education regarding CCTA performance characteristics for detection of CAD and risk stratification in suspected CAD and ED-based populations, as well as on radiation exposure levels from the test based on published data, was provided to clinicians at each site by the trial Principal Investigator in the form of Grand Rounds or presentations at staff meetings.

The study was designed by U.H. and the Steering Committee, the data collection and analysis was performed by an independent data and statistical center (PI: D.S.) who also vouches for the data and the analysis, the paper was drafted by U.H. and reviewed by all co-authors. The co-authors in conjunction with the publications committee (Chairman: S.W.) decided to publish the paper. There is an agreement concerning the confidentiality of the individual cost data between the sponsor and the authors and the institutions named in the credit lines.

The study protocol was reviewed and approved by the institutional review board at each participating center. The National Heart, Lung and Blood Institute (NHLBI) sponsored the study and trial conduct was overseen by an independent data and safety monitoring board appointed by NHLBI. An independent data coordinating center (D.A. S.) supported the data and safety monitoring board (DSMB) by performing interim analyses, including those proposed by the NHLBI (ClinicalTrials.gov ID: NCT01084239).

Study Protocol

In order to assess for enrollment bias, data regarding potential eligibility, age, gender, and ethnicity of patients presenting outside of study enrollment periods was collected over a two-week period (from 05/16/2011 to 05/29/2011), to compare to the enrolled population.

CCTA Imaging

Assessment of left ventricular function was optional, and reporting of incidental findings was mandated. CCTA images were interpreted on-site in real time, and results communicated to the responsible clinician. Before the trial began, CCTA readers at each site underwent training

for quality assurance, with a series of test cases provided by the trial Coordinating Center, and review of test interpretations and reporting style, as consistent with current Guidelines.¹

Results

Patients who were protocol eligible but not enrolled (n=228), were of similar age (53.7 ± 8.7 , $p=0.44$), but more likely female (47% vs. 60%, $p=0.0005$), and African American (28% vs. 39%, $p=0.002$). Patients who were found to be potentially protocol eligible during a screening period of two weeks outside of study enrollment period had similar demographics and rate of presentation to ED as enrolled patients, suggesting no enrollment bias was present.

CEC Charter - Definitions of Discharge Diagnosis, Missed ACS, and MACE

Discharge Diagnosis

For the definition of Acute Coronary Syndrome (MI or unstable angina) please refer to the definition of MACE. For non-cardiac chest pain, non coronary cardiac chest pain, and coronary chest pain not specified as Acute Coronary Syndrome we refer to the clinical judgment of the adjudicators using commonly applied definitions. While it is important to determine a discharge diagnosis of non-cardiac chest pain or chest pain not specified as Acute Coronary Syndrome, the adjudication for a specific differential can be difficult as this is often based on the absence of findings rather than a certain proven differential. Coronary chest pain not specified as ACS should be indicated when the most likely diagnosis for the patient is coronary ischemia, however the findings do not meet the severity criteria required for ACS. Thus, for the purposes of this adjudication, the choice of a differential can be based on the clinical judgment of the readers (i.e. highest probability w/o the necessity to have definite results of diagnostic tests etc. available).

Missed ACS

Missed ACS is a major adverse event and is defined as an unexpected Cardiac Ischemic Event within 72 hours of hospital discharge in patients discharged within 24 hours from index hospitalization.

Major Adverse Cardiovascular Events (MACE)

Major Adverse cardiovascular events comprise cardiovascular death, MI, unstable angina pectoris (UAP) and/or coronary revascularization that are distinct from the qualifying event (after patient's initial ED presentation). Note there is a possibility that MACE will occur during index hospitalization. For example, a second episode of chest pain diagnosed as acute coronary syndrome (ACS) occurring after the chest pain the patient presented with has resolved and all diagnostic tests were negative or recurrence of symptoms with or without hospitalization and re-hospitalization with or without testing.

Cardiovascular Death: Any sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes. In addition, any death without a clear non-cardiovascular cause, or a death without known cause will be considered cardiovascular death.

Myocardial Infarction: In subjects with no recent revascularization in whom normal biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI who meet the following criteria:

1. Typical cardiac biomarker rise and/or fall AND at least one of the following:
 - a) Ischemic discomfort at rest lasting ≥ 10 minutes
 - b) ECG changes indicative of ischemia (ST elevation ≥ 0.1 mV or ST depression ≥ 0.05 mV, or new T-wave inversions.

OR;

2. Development of new, abnormal Q waves (≥ 30 msec in duration and ≥ 1 mm in depth) in >2 contiguous precordial leads or ≥ 2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction.

OR;

3. Pathologic findings of an acute MI
4. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

In subjects with percutaneous coronary intervention within 48 hours, an elevation of CK-MB >3 x ULN distinct from a prior event will be considered to be a procedural MI.

In subjects with CABG within 48 hours, an elevation of CK-MB > 10 x ULN distinct from a prior event will be considered to be a procedural MI. For subjects with elevated cardiac biomarkers at the time of a suspected new event, the new event must be demonstrated to be distinct from a previous event including demonstration that cardiac biomarkers are falling and

that the new event is associated with a rise in biomarkers of at least 50% above a the previous value.

For each MI identified by the CEC, a Type of MI will be assigned using the following guidelines:

Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a: Myocardial infarction associated with PCI

Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5: Myocardial infarction associated with CABG

Unstable Angina: An event not meeting the definition of myocardial infarction and with the following characteristics. Chest pain or anginal equivalent at rest or in accelerating pattern AND at least one of the following objective signs:

- a. New and/or dynamic ST-depression ≥ 0.05 mV, ST-elevation ≥ 0.1 mV, or symmetric T wave inversion ≥ 0.2 mV on a resting ECG.

- b. Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy (e.g., an area of clear reversible ischemia), or ECG-only stress test (e.g., significant dynamic ST shift, horizontal or downsloping).
- c. Angiographic evidence of epicardial coronary stenosis of $\geq 70\%$ diameter reduction and/or evidence for intraluminal arterial thrombus.
- d. Positive stress test without imaging resulting in increased anginal medication
- e. CT angiography showing $> 50\%$ stenosis with regional LV dysfunction or $> 70\%$ stenosis.

Urgent Coronary Revascularization: Ischemic discomfort or equivalent meeting the following criteria:

- a. Lasting ≥ 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, considered to be myocardial ischemia upon final diagnosis

AND;

- b. Prompting coronary revascularization during an unscheduled visit to healthcare facility or during an unplanned (or prolonged) hospitalization for these symptoms.

Note: Attempted revascularization procedures, even if not successful will be counted. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as urgent coronary revascularization.

References

1. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2009;3:190-204.